Iranian Journal of Veterinary Science and Technology
Vol. 3, No. 2, 2011, 1-8

IJVST

The current rules on bluetongue vaccination in EU: from the origin to date

Maria Russo [1], Vincenzo Cuteri [2], Valeria Quartarone [3], Maria Cubeddu Giovanni [4], Giovanna Lai Maria [4], Annamaria Passantino [3*]

[1] University of Messina, Italy
[2]School of Medical Veterinary Sciences, University of Camerino, Italy
[3]Department of Veterinary Public Health, Faculty of Veterinary Medicine, University of Messina, Italy
[4]Department of Veterinary Pathology and Clinic, Faculty of Veterinary Medicine, University of Sassari, Italy

Received: August 20, 2011 Accepted: January 22, 2012

Abstract

The Council Directive 2000/75/EC lays down controlling rules and measures to contrast and to eradicate bluetongue disease, including rules on the establishment of protection and surveillance zones and the use of vaccines against bluetongue.

In the past years, only sporadic incursions of certain serotypes of the bluetongue virus were recorded in EU. However, after the adoption of the Directive, and particularly after the introduction into the Union of bluetongue viruses serotypes 1 and 8 in the years 2006-2007, the infection has become more widespread in EU, with the potential of becoming endemic in certain areas.

The rules of vaccination against bluetongue laid down in Directive 2000/75/EC are based on the experience of the use of so-called “modified live vaccines”, or “live attenuated vaccines” that were the only available vaccines when the Directive was adopted. The use of those vaccines may lead to an undesired local circulation of the vaccine virus, also in unvaccinated animals.

In recent years inactivated vaccines against bluetongue, which does not pose a risk for unvaccinated animals, have been introduced. The widespread use of these vaccines, during a vaccination campaign, led to a significant improvement in the disease situation. It’s now widely accepted that vaccination with inactivated vaccines is the preferred tool for the control of bluetongue and prevention of this clinical disease in EU.

In order to ensure the better control of the bluetongue virus spread, the Authors underline the necessity to amend the current rules on vaccination to take account of recent technological developments in vaccine production.

Keywords: vaccines, Bluetongue, rules; European Union

*Corresponding author: Annamaria Passantino
Email: passanna@unime.it
Tel: +39 090 3503742, +39 090 3503824

Introduction

Bluetongue (BT) is a vector-borne viral disease that is not contagious, which affects sheep and other domestic and wild ruminants, caused by an *Orbivirus* (family *Reoviridae*) that consists of 24 serotypes clustered within 10 distinct lineages (Schwartz-Cornil *et al*., 2008), whose vector is a small blood-feeding midge of the genus *Culicoides* (family *Ceratopogonidae*).

Culicoides imicola was believed to be the only vector of BT in both Africa and southern Europe (Guyot *et al*., 2007), but it is known that other newly identified (and yet unidentified) vectors are involved like *Culicoides dewulfi*, *Culicoides chiopterus* and members of the Obsoletus and Pulicaris complexes. Possible factors that have contributed to the spread of BT virus (BTV) include animal trade and importation, extension in the distribution of its major vector, *Culicoides* spp., the apparent ability of the virus to overwinter in the absence of adult vectors, and its occurrence in healthy reservoir hosts, such as cattle and, out of Europe, some wild ruminants (Takamatsu *et al*., 2003; Dungu *et al*., 2004; Purse *et al*., 2005).

Historically, it was thought that the Bluetongue virus (BTV) had evolved and was contained within Africa until the 1940s, when the first Mediterranean outbreak occurred in Cyprus. However, consequent studies have found that BTVs were widely distributed in the tropics but not usually associated with illness and therefore were mostly undetected (Gibbs *et al*., 1992; Gibbs *et al*., 1994). Clinical disease most prevalent in domestic sheeps, especially those of European ancestry (Purse *et al*., 2008). Cattles rarely show clinical illnesses and typically are considered a reservoir host, whereas goats usually do not develop evident diseases (Gibbs and Greiner, 1988); however, during the recent incursion of serotype 8 into Western Europe, clinical illness in cattle was common but associated with a low fatality rate (Weaver and Reisen, 2010). BT is a notifiable disease of the World Organization for Animal Health (OIE), and is of serious socio-economic concern and of major importance in the international trade of animals and biological products, like semen and embryos (Dungu *et al*., 2004; OIE, 2010).

The epidemiology of BTV in Europe is complex and related strongly to virus and vector genetics and distributions, overwintering mechanisms, and perhaps climate changes. BT situation in the EU has considerably changed in recent times with incursions of new serotypes, namely of serotype 8 (in an area of the Community where outbreaks have never been reported before and which was not considered at risk of BT) and also of serotype 1 in southern Europe (EFSA, 2007; Mac Lachlan, 2010). In fact, in August 2006, several Northern European countries reported the first ever outbreaks of BT, including The Netherlands, Belgium, Germany and France (Table 1). In 2007 and 2008, further outbreaks, involving also the UK and Sweden, were reported.

Introductions and subsequent dispersals of BTV most likely will continue due to intercontinental animal and biological product commerce as well as through windborne dispersal of infected midges (Sellers, 1980; Hendrickx *et al*., 2008). Global warming most likely will expand the epizootic zone into northern temperate regions and move the zone of incursion further northwards, out of Europe too.

BT control is generally based on a combination of vaccination, protection from vectors, restrictions on animal movements and slaughter of infected animals especially in free areaswhere local vectors are not involved, and eventually molecular engineering/selective breedings of livestock to increase resistance to diseases. Molecular biology may hold the answer if current susceptible breeds of cattle and sheep can be genetically modified to impart resistance. Treating wastewater ponds or other known larval habitats and the control of *Culicoides* that develop in less obvious habitats such as moist pastures will be a much greater challenge, especially in Europe.

Chemical dips have been used to control tick infestations and perhaps a similar approach with other compounds could be used to reduce or eliminate adult midges or prevent biting, even if actual available repellent products have a short life. Complex immune interactions against as many as 24 serotypes makes vaccine development challenging, but perhaps vaccines can be developed against specific strains of BTV with a particularly high potential for invasion (Weaver and Reisen, 2010).

Under the current rules, the use of vaccines against BT is prohibited outside "restricted zones". Consequently, Member States (MSs) that wish to carry out preventive vaccination must either retain a restricted zone beyond the two years of absence of virus circulation, while other MSs decide to become part of a restriction zone although BT has never occurred. This situation leads to unnecessary restrictions in the concerned areas with additional burdens for the farmers and the national authorities.

In the past three years inactivated vaccines against BTV have become available which could be safely used outside restricted zones. The provisions on vaccination against BTV should therefore be amended to allow the MSs to develop their national strategies on the prevention and control of the infection without the unnecessary intervention of the Union.

In order to ensure the better control of the BTV spread, the Authors underline the necessity to amend the current rules on vaccination to take account of the recent technological developments in vaccine production.

Background

EU control measures to contrast BT are in place since the year 2000 through Council Directive 2000/75/EC, (EC, 2000) including the establishment of protection and surveillance zones and a ban on susceptible animal species leaving those zones. This Directive lays down rules on vaccination against the disease.

These rules are based on experiences with the so-called “modified live vaccines”, or “live attenuated vaccines” that were the only vaccines available when the Directive was adopted a decade ago. Those vaccines may lead to undesired circulation of the vaccine virus in unvaccinated animals in the areas where the vaccine has been used (Savini *et al*., 2008). However, in the last few years inactivated vaccines have been developed by several pharmaceutical companies and largely used in the EU. These inactivated vaccines do not pose the risk of undesired vaccine virus circulation.

Further controling rules have been adopted to tackle the recent outbreak through coordinated European action.

Implementation measures of Directive 2000/75/EC are established on Commission Regulation No. 1266/2007/EC (EC, 2007) that contains detailed implementing rules for the control, monitoring, surveillance of animals and flying midge insects plus restrictions on the movement of certain animal species.

The Regulation amended certain existing EU measures for BT, to make them more sustainable, proportionate and science-based. It brings EU rules more into line with international standards and reduces as far as possible obstacles to trade that BT may cause while maintaining the adequate level of guarantees.

Commission Decision 2008/655/EC of July 24, 2008 approves the vaccination plans against BT in Belgium, Czech Republic, Denmark, Germany, Spain, France, Italy, Luxemburg, the Netherlands and Portugal and establishes the maximum amount of the Community financial contribution for the year 2008 (EC, 2008). This Decision has been amended by Commission Decision 2009/19/EC approving the newly submitted vaccination plans of Austria and Sweden and the amended plans of Denmark, Spain, France, the Netherlands and Portugal, thus establishing new maximum amounts of the Community financial contribution for the MSs (EC, 2009).

Commission Regulation (EC) No.

1266/2007 of October 26, 2007, on implementing rules for Council Directive 2000/75/EC as regards the control, monitoring, surveillance and restrictions on movements of certain animals of susceptible species in relation to BT - amended several times - provides for an amended regulatory framework on BT that entered into force on November 1, 2007 (EC, 2007). This Regulation has been drawn up on the basis of experience gained and the scientific advice that has already been provided by recent EFSA opinions to the Commission supporting the legislative decision making process and risk management. The Regulation amended certain existing EU measures for BT, to make them more sustainable, proportionate and science-based. It brings EU rules more into line with international standards and reduces as far as possible obstacles to trade that the disease may cause while maintaining the adequate level of guarantees.

Vaccination as a strategic solution

Vaccination is an important tool for the control of BTV infection and is also used to permit ‘safe’ trade in live ruminants based on EU legislation and in accordance with OIE standards.

First it should be noted that there are two major problems with current bluetongue vaccines. The first relates to the implementation of vaccination as a means to control bluetongue in livestock. Animal movement controls necessitate the distinction between infected and vaccinated animals (DIVA) (Barros *et al*., 2009). This is mostly important in the case of BT-infected cattle, which can be asymptomatic but viraemic, and can therefore act as potential source of infection if moved to a new area. Current vaccines do not yet address this problem. Secondly, BT is not immunologically simple. The virus is present as 24 different serotypes, and protection afforded by vaccines is specific according to serotype. Thus, an animal vaccinated with one serotype of bluetongue is not protected from infections with other viral serotypes (Noada *et al*., 2009).

There is currently no published data on whether there is interference in protection afforded to different serotypes in polyvalent vaccines beyond fairly simple bivalent preparations.

However, there is some data from recombinant experimental vaccines that a limited amount of cross protection between serotypes may be afforded by certain combinations of immunogens.

Usually multiple serotype of the virus are common in enzootic areas, so multivalent vaccines are required to prevent multiple incursions of different serotypes into previously bluetongue-free areas (Bhanuprakash *et al*., 2009). South African scientists were the first to develop BT vaccines in 1940, and Onderstepoort Biological Products is the only producer of live attenuated BT vaccines. Currently the vaccines against BTV are inactivated and live attenuated, while are in progress recombinant, virus-vectored and chimeric vaccines (Noada, 2009).

The inactivated vaccines are usually prepared with BTV, killed with several techniques or products, associated with different adjuvants. The production and use of inactivated vaccines in EU started against BTV2, followed by BTV4 and a bivalent BTV2 and 4 and BTV1 and 8. Recently an inactivated vaccine against BTV8, adjuvanted with aluminum hydroxide and saponin, has been developed and is available in EU. Different animal species have been vaccinated in the EU, depending on each individual country’s police. In Italy all the susceptible domestic animals, including sheep, goat, cattle and buffalo, have been allowed to be vaccinated against BT. Inactivated BT vaccine are safe but are beset by contraindication, including the possibility of incomplete inactivation, the requirement for booster and the cost of production (Bhanuprakash *et al*., 2009). The advantages include the absence of replicating virus and viremia, reversion to virulence, and teratology during pregnancy.

The attenuated live vaccines are officially produced in agreement to national and international standards complying purity, safety, efficacy and potency. However millions of sheep, goat, cattle and buffaloes have been vaccinated with monovalent, bivalent, trivalent, polyvalent or pentavalent attenuated vaccines in different EU countries from 1999 to 2006 with inconsistent safety results. The potential adverse impact is known to be dependent on the specific formulation used, specific serotype and the number of serotypes included in the vaccine. Fever, edema, lameness and abortion were the main symptoms that could be observed after vaccination (Noada, 2009; Savini *et al*., 2008).

Regarding recombinant vaccines, recent developments in molecular biology techniques have allowed the development of new vaccines composed of synthetically produced virions with similar characteristics to the original viral particles but with lack of the ability to replicate. While experiments conducted in South Africa looked promising, tests made in Italy have shown the total ineffectiveness of this type of vaccines. Clearly, further studies are needed to demonstrate the effectiveness of these products (Savini *et al*., 2008).

Immunization of sheep and goat with recombinant BTV-capripoxvirus expressing the capsid proteins VP2 and VP7 and the unstructural proteins NS1 and NS3 of BTV have been found to be effective but further studies are yet necessary (Noada, 2009).

Concluding remarks

Vaccination against BTV is an important tool for control of the disease and for safe trade of live ruminants in accordance to OIE standard and EU legislation (Patta *et al*., 2004).

For safety reasons the use of inactivated vaccines would be preferable. Since 2005 BTV inactivated vaccines have been in the market and used in vaccination campaigns in Italy, France, Spain and Portugal (Savini *et al*., 2009).

The tentative control of BT in Europe by vaccination should ideally be based on the use of live attenuated vaccines that include local strains. This would avoid the possible introduction of new BTV topotypes from different ecosystems (e.g. South Africa), in case vaccine strains revert to virulence. The type of vaccine used would depend on the BTV serotype(s) (mono-, bi- or trivalent) prevalent in EU countries and in countries bordering the Mediterranean Sea and which are liable to affect the nearby parts of the EU.

In the opinion of the Authors, the revision of the legislation is necessary to reflect the technological progress in the field of vaccine development. The current obstacles for preventive vaccination outside areas subjected to animal movement restrictions are not necessary when modern safe "inactivated vaccines" are used.

The proposed revision could be facilitate decision making on BT control strategies on the basis of the specific situation within the MSs without unnecessary intervention by the Union.

In conclusion, the introduction of mentioned rules above on vaccination is in line with the Animal Health Strategy (2007-2013) “Prevention is better than cure”, as it moves towards a more flexible approach to vaccination, as well as improving current measures to control major animal diseases.

References

Barros, S.C., Cruz, B., Luis, T.M., Ramos, F., Fagulha, T., Duarte, M., Henriques, M., Fevereiro, M. (2009) A DIVA system based on the dectetion of antibodies to non-structural protein 3 (NS3) of bluetongue virus. *Veterinary Microbiology* **137**(1-2), 252-259.

Bhanuprakash, V., Indrani, B.K., Hosamani, M., Balamurugan, V., Singh, R.K. (2009) Bluetongue vaccine: the past, present and future. *Expert Review* of *Vaccines* **8**(2), 191-204.

Dungu, B., Gerdes, T., Smit, T. (2004) The use of vaccination in the control of bluetongue in southern Africa.

Veterinaria Italiana **40** (4), 616-622.

EC (2000) Council Directive 2000/75/EC of 20 November 2000 laying down specific provisions for the control and eradication of bluetongue. *Official Journal of the European Union* L 327 of 22.12.2000, p.74.

EC (2007) Commission Regulation No. 1266/2007 of 26 October 2007 on implementing rules for Council Directive 2000/75/EC as regards the control, monitoring, surveillance and restrictions on movements of certain animals of susceptible species in relation to bluetongue. *Official Journal of the European Union* L 283 of 27.10.2007, 37-52.

EC (2008) Commission Decision of 24 July 2008 approving the emergency vaccination plans against bluetongue of certain Member States and fixing the level of the Community's financial contribution for 2007 and 2008. *Official Journal of the European Union* L 214 of 9.8.2008, 66-69.

EC (2009) Commission Decision of 9 January 2009 amending Decision 2008/655/EC as regards the approval of the emergency vaccination plans against bluetongue of certain Member States and fixing the level of the Community's financial contribution for 2007 and 2008. *Official Journal of the European Union* L 8 of 13.1.2009, 31-32.

EFSA (2007) Epidemiological analysis of the 2006 bluetongue virus serotype 8 epidemic in north-western Europe. *EFSA Journal*, 1-35. Available at http://www.efsa.europa.eu/en/supporting/doc/34br.pdf

EFSA (2008) Bluetongue vectors and insecticides Scientific Opinion of the Panel on Animal Health and Welfare. *The EFSA Journal* 735, 1-70.

Gibbs, E.P.J., Greiner, E.C. (1988) Bluetongue and epizootic hemorrhagic disease. In: Monath, T.P. (Ed.), The Arboviruses: Epidemiology and Ecology, vol. II. CRC Press, Boca Raton, FL, pp. 39-70.

Gibbs EP, Homan EJ, Mo CL, Greiner EC, Gonzalez J, Thompson LH, Oveido MT, Walton TE, Yuill TM. (1992) Epidemiology of bluetongue viruses in the American tropics. Regional Bluetongue Team. *Annals of the New York Academy of Sciences* **653**, 243-250.

Gibbs, E.P.J., Greiner, E.C. (1994) The epidemiology of bluetongue. *Comparative Immunology, Microbiology and Infectious Diseases* **17**(3-4), 207-220.

Guyot, H., Mauroy, A., Thiry, E., Losson, B., Bodmer, M., Kirten, P., Rollin, F., Saegerman, C. (2007) Fièvre catarrhale ovine chez les ruminants. Description clinique des cas vécus dans le Nord de l'Europe durant l'été et l'automne 2006. *Bulletin GTV* **39**, 89-96.

Hendrickx, G., Gilbert, M., Staubach, C., Elbers, A., Mintiens, K., Gerbier, G., Ducheyne, E. (2008) A wind density model to quantify the airborne spread of Culicoides species during north-western Europe bluetongue epidemic, 2006. *Preventive Veterinary Medicine* **87**, 162-181.

MacLachlan, J.N., Guthrie, A.J. (2010) Re-emergence of bluetongue, African horse sickness, and other Orbivirus diseases. *Veterinary Research* **41**, 35.

Noada, R., Roy, P. (2009) Bluetongue vaccines. Vaccine 27, D86-D89.

World Organisation for Animal Health (OIE) (2010) Terrestrial Animal Health Code, Chapter 8.3. Bluetongue. http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.8.3.htm, accessed on 3-05-2011.

Patta, C., Giovannini, A., Rolesu, S., Nannini, D., Savini, G., Calistri, P., Santucci, U., Caporale, V. (2004) Bluetongue vaccination in Europe: the Italian experience. *Veterinaria Italiana* **40**(4), 601-610.

Purse, B.V., Mellor, P.S., Rogers, D.J., Samuel, A.R., Mertens, P.P., Baylis, M. (2005) Climate change and the recent emergence of bluetongue in Europe. *Nature Reviews Microbiology* **3** (2), 171-181.

Purse, B.V., Brown, H.E., Harrup, L., Mertens, P.P., Rogers, D.J. (2008) Invasion of bluetongue and other orbivirus infections into Europe: the role of biological and climatic processes. *Revue Scientifique Et Technique* **27**, 427-442.

Savini, G., MacLachlan, N.J., Sanchez-Vizcaino, J.M., Zientara, S. (2008) Vaccines against bluetongue in Europe. *Comparative Immunology, Microbiology and Infectious Diseases* **31**(2-3), 101-120.

Savini, G., Hamers, C., Conte, A., Migliaccio, P., Bonfini, B., Teodori, L., Di Ventura, M., Hudelet, P., Schumacher, C., Caporale, V. (2009) Assessment of efficacy of a bivalent BTV-2 and BTV-4 inactivated vaccine by vaccination and challenge in cattle. *Veterinary Microbiology* **133**(1-2), 1-8.

Schwartz-Cornil, I., Mertens, P.P., Contreras, V., Hemati, B., Pascale, F., Breard, E., Mellor, P.S., MacLachlan, N.J., Zientara, S. (2008) Bluetongue virus: virology, pathogenesis and immunity. *Veterinary Research* **39**, 46.

Sellers, R.F. (1980) Weather, host and vector - their interplay in the spread of insect-borne animal virus diseases. *The Journal of Hygiene* **85**(1), 65-102.

Takamatsu, H., Mellor, P.S., Mertens, P.P.C., Kirkham, P.A., Burroughs, J.N., Parkhouse, R.M.E. (2003) A possible overwintering mechanism for bluetongue virus in the absence of the insect vector. *Journal of General Virology* **84**, 227-235.

Weaver, S.C., Reisen, W.K. (2010) Present and future arboviral threats. *Antiviral Research* **85**(2), 328-345.

Iranian Journal of Veterinary Science and Technology
Vol. 3, No. 2, 2011, 1-8

IJVST

قوانین رایج در مورد بیماری زبان آبی در اروپا، از ابتدا تا کنون

ماریا روسو [۱]، وینچنزو کوتری [۲]، والریا کارتارونه [۳]، ماریا کوبدو جیووانی [۴]، جیووانا لای ماریا [۴]، آناماریا پاسانتینو [۳*]

[۱] دانشگاه مسینا، ایتالیا
[۲] دانشکده دامپزشکی، دانشگاه کامرینو، ایتالیا
[۳] گروه بهداشت، دانشکده دامپزشکی، دانشگاه مسینا، ایتالیا
[۴] گروه پاتولوژی دامپزشکی و بالینی، دانشکده دامپزشکی، دانشگاه ساساری، ایتالیا

دریافت مقاله: ۱۳۹۰/۵/۲۹ پذیرش نهایی: ۱۳۹۰/۱۱/۲

چکیده

بخشنامه EC/۷۵/۲۰۰۰ ، قوانین و رویکردهای مرتبط با نحوه کنترل و ریشه کنی بیماری زبان آبی را مدون و مشخص می‌سازد، از جمله مقررات مربوط به ایجاد مناطق حفاظت و نظارت و استفاده از واکسن علیه بیماری زبان آبی.

در سال‌های گذشته، تنها رخدادهای پراکنده از سروتیپ های خاصی از ویروس بیماری زبان آبی در اروپا ثبت شده است. با این حال، پس از تصویب بخشنامه، و به‌ویژه پس از رخداد سروتیپ‌های ۱ و ۸ ویروس بیماری زبان آبی در حوزه اتحادیه اروپا در سال ۲۰۰۶–۲۰۰۷، عفونت به شکل گسترده‌تری در اتحادیه اروپا در آمده و پتانسیل بومی شدن در برخی مناطق خاص را پیدا کرده است.

مقررات واکسیناسیون علیه بیماری زبان آبی که در دستورالعمل EC/۷۵/۲۰۰۰ آمده است بر اساس تجربیات استفاده از به اصطلاح "واکسن‌های زنده تغییر یافته"، و یا "واکسن‌های زنده تخفیف حدت یافته" بوده که که در زمان تصویب دستورالعمل، تنها واکسن‌های در دسترس بودند. استفاده از چنین واکسن‌ها ممکن است منجر به گردش نامطلوب ویروس واکسن در منطقه و نیز در حیوانات واکسن نخورده شود.

در سال‌های اخیر واکسن‌های غیر فعال، که فاقد اینگونه خطرات برای حیوانات واکسن نخورده هستند، معرفی شده‌اند. استفاده گسترده از این واکسن در طی برنامه‌های واکسیناسیون، منجر به بهبود قابل توجهی در وضعیت بیماری شده است. در حال حاضر به طور گسترده پذیرفته شده است که واکسیناسیون با واکسن غیر فعال، ابزار ارجح برای کنترل بیماری زبان آبی و پیشگیری از این بیماری در اروپا است.

به منظور حصول اطمینان از کنترل بهتر گسترش ویروس بیماری، نویسندگان این مقاله بر ضرورت اصلاح قوانین موجود در واکسیناسیون به منظور بهره گیری از پیشرفت‌های اخیر تکنولوژیک در تولید واکسن تکیه دارند.

واژگان کلیدی: واکسن، زبان آبی، قوانین، اتحادیه اروپا